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Review

Apolipoprotein A-II is a key regulatory factor of HDL metabolism as appears from studies with transgenic animals and clinical outcomes

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ABSTRACT

The structure and metabolism of HDL are linked to their major apolipoproteins (apo) A-I and A-II. HDL metabolism is very dynamic and depends on the constant remodeling by lipases, lipid transfer proteins and receptors. HDL exert several cardioprotective effects, through their antioxidant and antiinflammatory capacities and through the stimulation of reverse cholesterol transport from extrahepatic tissues to the liver for excretion into bile. HDL also serve as plasma reservoir for C and E apolipoproteins, as transport vehicles for a great variety of proteins, and may have more physiological functions than previously recognized. In this review we will develop several aspects of HDL metabolism with emphasis on the structure/function of apo A-I and apo A-II. An important contribution to our understanding of the respective roles of apo A-I and apo A-II comes from studies using transgenic animal models that highlighted the stabilizatory role of apo A-II on HDL through inhibition of their remodeling by lipases. Clinical studies coupled with proteomic analyses revealed the presence of dysfunctional HDL in patients with cardiovascular disease. Beyond HDL cholesterol, a new notion is the functionality of HDL particles. In spite of abundant literature on HDL metabolic properties, a major question remains unanswered: which HDL particle(s) confer(s) protection against cardiovascular risk?

1. Introduction

High density lipoproteins (HDL) are the smaller-sized lipoproteins that exert several protective actions against cardiovascular diseases (CVD), as first suggested by Miller and Miller [1]. Notably, HDL stimulate reverse cholesterol transport (RCT) from peripheral tissues to the liver, and display antioxidant, antiinflammatory and antithrombotic capacities. Epidemiological studies have also established that a low plasma HDL concentration is a risk factor for CVD [2]. The metabolism of HDL is complex and closely related to that of triglyceride (TG)-rich lipoproteins (TRL). An important point is that HDL are not assembled in cells and secreted in the circulation as discreet particles; instead, HDL are formed in the extra-cellular space of organs (essentially liver and intestine), and mature in plasma where they are subjected to intense remodeling [3]. HDL catabolism also follows a unique course, in that their cholesterol and protein components are catabolized in great part separately from the HDL particle (thereafter termed holoparticle). Today, several aspects of HDL holoparticle catabolism remain unclear despite intense investigations. An additional complexity is that HDL constitute an heterogeneous population of particles of various sizes and carrying different apolipoproteins, apo A-I and apo A-II being their major apolipoproteins [4,5]. HDL have the longest plasma half-life of all lipoprotein classes and serve as a reservoir for apolipoproteins such as apo C's and apo E that play crucial roles in TRL catabolism [6]. Beyond lipid transport, HDL fulfill a vehicle function

Abbreviations: ABCA1, ATP binding cassette transporter A1; ABCG1, ATP binding cassette transporter G1; apo, apolipoprotein; apo B-LP, apo B-containing lipoproteins; CE, cholesterol ester; CETP, CE transfer protein; CVD, cardiovascular diseases; d, density; EL, endothelial lipase; FA, fatty acid; FC, free cholesterol; hapo A-I, human apo A-I; hapo A-II, human apo A-II; HDL, high density lipoproteins; HL, hepatic lipase; HSPG, heparan sulfate proteoglycans; KO, knockout; LCAT, lecithin-cholesterol-acyltransferase; LPL, lipoprotein lipase; mapo A-II, murine apo A-II; MI, myocardial infarction; PAF-AH, platelet-activating factor acetylhydrolase; PL, phospholipid; PLTP, PL transfer protein; PON1, paraoxonase 1; RCT, reverse cholesterol transport; rHDL, reconstituted HDL; SR-BI, scavenger receptor class B type I; TG, triglyceride; TICE, transintestinal cholesterol excretion; TRL, TG-rich lipoproteins.

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for several cargo proteins, as unveiled by proteomic studies [7,8]. HDL are considered as new therapeutic targets and several investigations attempted to raise their plasma concentration. However, new concepts have emerged: i) the functionality/nature of HDL particles is better linked to atheroprotection than total plasma HDL-cholesterol concentration; ii) HDL particles may become dysfunctional and lose their atheroprotective properties.

This review will compare the respective roles of apo A-I and apo A-II on HDL metabolism and stress their synergistic effects, based on transgenic animal models and clinical studies.

2. Heterogeneity of HDL particles: importance of the major apolipoproteins apo A-I and apo A-II

The classical ultracentrifugation technique provided the first means to obtain relatively pure samples of individual lipoproteins and thus study their composition [9]. Apo A-I and apo A-II represent 70 and 20% (by weight) of total HDL proteins, respectively and apo A-IV, apo C's (CI, CII and CIII) and apo E are minor HDL apolipoproteins [3,5]. Most HDL particles have a buoyant density (d) between 1.063 and 1.21 g/ml and have been classified in two subclasses: HDL_2 ($1.063 < d < 1.125$ g/ml) and HDL_3 ($1.125 < d < 1.210$ g/ml). An excellent review provides an up to date survey and critical evaluation of all methods of analysis of HDL particles [10], such as: i) gradient gel electrophoresis identifying five HDL subspecies on the basis of particle diameter: HDL3c (7.2–7.8 nm), HDL3b (7.8–8.2 nm), HDL3a (8.2–8.8 nm), HDL2a (8.8–9.7 nm) and HDL2b (9.7–12.9 nm); ii) non denaturing two-dimensional gel electrophoresis followed by immunoblotting for apo A-I separating HDL on the basis of size and charge into particles with α or pre-β mobility. Five major HDL particles were identified: very small discoïdal pre-β1 and α-4 particles, small spherical α-3, medium-sized spherical α-2 and large spherical α-1 particles. Apo A-I was present in all five particles, whereas apo A-II was present in midsize α-3 and α-2 particles and very little in α-1 particles. A major breakthrough in understanding the functional heterogeneity of HDL (and all other lipoproteins as well) came early on from P. Alaupovic who classified HDL subpopulations according to their apolipoprotein content [4] by use of immunoaffinity chromatography. By this technique HDL were separated into particles containing: only apo A-I (LpAI), both apolipoproteins (LpAI:AII) and only apo A-II (LpAII), a minor subpopulation [10,11].

Apo A-I is a single-polypeptide chain of 28 kDa, containing 243 amino acids and lacking glycosylation and disulfide linkages [for review, [12] and references therein]. Apo A-II in humans (and chimpanzees, but not in other species) circulates in plasma as a homodimer of 17.4 kDa, consisting of two identical polypeptide chains of 77 amino acid residues covalently linked by a single disulfide bond formed by Cys6. Physicochemical studies established the degree of hydrophobicity of apo A-I, apo A-II and all other exchangeable apolipoproteins, that is associated with their individual binding affinities to small unilamellar phospholipid (PL) vesicles. It was shown that apo A-II is more hydrophobic than apo A-I and, upon an increase in dimeric apo A-II concentration, it displaces apo A-I in vitro from the surface of HDL [12]. An additional question was whether the monomeric or dimeric nature of apo A-II modifies its structural properties. Reduction of the Cys6–Cys6 disulfide bridge did not affect the size distribution of reconstituted HDL particles in vitro, but somewhat decreased the stability of the helical segments [13].

Apolipoproteins have amphipathic properties due to a common structural motive, the α-helix. The pioneering studies of J. Segrest opened the way to a better understanding of the properties of α-helices and the secondary structure of apolipoproteins [14]. The recent combination of computer models and the crystal structure of lipid-free (Δ185–243) apo A-I supported the double-belt conformation of apo A-I structure on discoidal reconstituted HDL (rHDL) particles [15]. Another study using chemical cross-linking and mass spectrometry predicted that apo A-I adopts a cage-like structure in spherical plasma HDL and suggested that HDL particle size is modulated via a twisting motion of resident apo A-I [16]. Investigation of the apo A-II structure in discoidal rHDL using chemical cross-linking/mass spectrometry and infrared spectroscopy supported a "double hairpin" conformation [17]. O. Gursky's team proposed the following roles of apo A-II in the structure and remodeling of HDL: i) endogenous apo A-II helps confer lipid surface curvature during conversion of nascent discoidal AI–HDL and AII–HDL to mature spherical AI/AII–HDL by hindering the expansion of the apo A-I conformation; ii) endogenous apo A-II circulates mainly on the midsize spherical AI/AII–HDL; iii) exogenous apo A-II can bind to HDL of any size, slightly increasing this size and stabilizing HDL [18]. In apo A-II, the apolar lipid-binding face comprises ~50% of the α-helical surface, as compared to ~30% in apo A-I. As a consequence, apo A-II inserts more deeply into the surface PL, conferring 2D surface curvature and stabilizing HDL. Addition of apo A-II to discoidal AI-rHDL induced conformational changes in helices 3–4 and 7–9 of apo A-I [19]. More studies are needed to explore the changes induced by apo A-II in mature spherical HDL.

3. HDL formation and maturation depend on ABCA1, LCAT and lipid transfer by the combined actions of LPL and PLTP

Early studies in rats reported formation of discoidal HDL particles by liver and intestine, nascent HDL particles being detected in liver perfusion media [20] and in mesenteric lymph, respectively [21]. In 1999, the discovery of ATP binding cassette transporter A1 (ABCA1), a membrane protein of ubiquitous expression, established its rate-limiting role in the first step of HDL formation [[22,23] for reviews]. In cultured murine hepatocytes, newly synthesized apo A-I is secreted bound to PL, binds extracellularly to ABCA1, acquires membrane free cholesterol (FC) and forms nascent HDL particles with pre-β mobility [24]. In hepatoma cell lines HepG2 and HuH7, apo A-II is lipidated and dimerizes intracellularly and is secreted in nascent HDL particles [25]. In the medium, the discrete apo A-II–HDL fuse with apo A-I–HDL forming A-I/A-II–HDL particles (Fig. 1).

Tissue-specific invalidation of ABCA1 established that liver and intestine account, respectively, for ~70% and ~20% of plasma HDL [26], whereas adipose tissue, which contains a large pool of FC, may contribute up to 15% of plasma HDL–cholesterol [27].

Although macrophages contribute little to plasma HDL levels [28], ABCA1-mediated cholesterol efflux to lipid-poor apolipoproteins is a key event to protect macrophages adherent in the vessel wall from excessive cholesterol accumulation, ultimately leading to atherosclerosis (details in Section 6).

Nascent HDL maturation begins with the action of lecithin-cholesterol-acyltransferase (LCAT), an enzyme primarily found on HDL and catalyzing a trans-esterification reaction involving the transfer of a fatty acid (FA) at the sn −2 position of phosphatidylcholine to the free hydroxyl group of cholesterol [29]. The net result is transfer of cholesterol ester (CE) to the HDL core and transformation of discoidal HDL to spherical ones, while phosphatidylcholine is converted into lysophosphatidylcholine. LCAT promotes in vitro fusion of rHDL containing only apo A-I (A-I rHDL) with rHDL of similar size containing only apo A-II (A-II rHDL), to form spherical A-I/A-II rHDL [25,30]. This process is also operative in vivo and may be an important source of A-I/A-II HDL in human plasma, since spherical HDL are absent in plasma of LCAT-deficient patients [29]. Apo A-I is the most potent activator of LCAT, followed by apo C-I and apo A-IV, whereas apo A-II neither activates nor inhibits LCAT activity [31]. Nonetheless, apo A-II can indirectly inhibit LCAT activity,